PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

STEPHEN M. ALLEN ET AL.

CASE NO: BB1157 US CNT

SERIAL NO: 10/659,199

GROUP ART UNIT: 1638

FILED: SEPTEMBER 10, 2003

EXAMINER: KUBELIK, ANNE R.

FOR: A NUCLEIC ACID ENCODING A WHEAT BRITTLE-1 HOMOLOG

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P.O. Box 1450
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APPEAL BRIEF under 37 C.F.R. 41.37

Sir or Madam:

Pursuant to 37 C.F.R. § 1.192, the following is an Appeal Brief in support of the Appeal filed April 2, 2009, appealing the Final Office Action dated 3-23-2009. Submitted herewith is the filing fee for this Appeal Brief in accordance with 37 C.F.R. § 41.20(b)(2). Please charge said fee, including any required extension of time or other required fee, to Deposit Account No. 04-1928 (E.I. du Pont de Nemours and Company).

I. REAL PARTY IN INTEREST

The real party in interest is E.I. du Pont de Nemours and Company (*hereinafter* "DuPont"), owner of the Application.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Applicants, Applicants' legal representative, or DuPont that will directly affect or be directly affected by or have a bearing on the Board of Patent Appeals and Interferences' (*hereinafter* the "Board") decision in the present Appeal.

III. STATUS OF THE CLAIMS

Claims 26-30 stand rejected and are the subject of this Appeal. Originally-filed Claims 1-25 have been canceled.

IV. STATUS OF AMENDMENTS

Claim 30 was added and claim 26 was modified in the response after final on 3-2-09 but the rejections remained exactly the same. Further, Applicant argues that these claims are twice rejected as they are simply species within the broader genus of claims which have been continually rejected in this case. Additionally, Examiner agrees as Examiner did not comment on the new claims or amendments in the Advisory Action, nor were any rejections modified in response to the claim amendments or new claim.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 26 and claim 30, the only independent claims at issue, relate to an isolated polynucleotide comprising: (a) a nucleotide sequence encoding a polypeptide having brittle-1 activity (*see, e.g.*, Applicants' Specification at page 6, lines 17-21), wherein the polypeptide has an amino acid sequence of at least 95% (or 100% in claim 30) sequence identity when compared to SEQ ID NO:18 (*see, e.g.,* Applicants' Specification at page 8, line 34 – page 9, line 17; page 14, lines 16-36), or (b) a full-length complement of the nucleotide sequence of (a) (*see, e.g.,* Applicants' Specification at page 8, lines 19-33; page 12, lines 3-7).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 26-30 are supported by sufficient written description under 35 U.S.C. § 112, 1st Paragraph.

Whether claims 26-30 are enabled under 35 U.S.C. § 112, 1st Paragraph.

Whether claims 26-30 are obvious under 35 U.S.C. § 103.

VII. ARGUMENT

Applicant believes the Office has not applied either the guidance from the Office or the BPAI holdings on Written Description and Enablement appropriately. The instant invention cites to specific references showing possession, and enabled one of skill in the art (see below). Applicant has fulfilled all requirements under 112 under any standard, but specifically those enunciated by the Board in *Ex parte Kubin* (Appeal 2007-0819 (BPAI May 31, 2007), *available at* http://www.uspto.gov/web/offices/dcom/bpai/prec/fd070819.pdf (last visited Oct. 9, 2007).

The instant invention is also differentiated from *In re Kubin* (Fed. Cir. 2008-1184, serial number 09/667859) on obviousness. The instant facts are very different from those in *Kubin* (see below). Further, the *Kubin* facts show a specific motivation to isolate the gene of interest. *Id* at 17. Herein, the Office can point to no specific motivation in any reference.

A. Claims 26-29 Comply with the Written Description Requirement of 35 U.S.C. § 112, 1st Paragraph.

Applicant assumes that based on the argument in the Advisory Action that only independent claim 26 (and those depending threrefrom) are rejected under 112 as the Applicant has clearly provided a sequence 100% identical to itself (see claim 30) and thus provided both Written description and Enablement for that claim under even the incorrect standard currently posited by the Office.

Claims 26-29 stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. During the course of prosecution,

the Examiner asserted that "the specification must teach the structural elements of the protein that confer Brittle-A activity." Advisory Action dated 3/23/2009 ("Advisory Action"). Applicant believes this is not the appropriate legal standard and that Applicants invention conforms with both the guidance provided by the Office in the Written Description Guidelines (see below) and the current standard for biological inventions forwarded by the BPAI in *Ex parte Kubin* (Appeal 2007-0819 (BPAI May 31, 2007), *available at* http://www.uspto.gov/web/offices/dcom/bpai/prec/fd070819.pdf (last visited Oct. 9, 2007) (see below). In fact, *Kubin* argues the opposite of this standard as it states "[p]ossession may **not** be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." (emphasis added).

Examiner further argues that "The correlation between DNA sequences and Brittle-1 activity is not well known, and not described in the specification." Applicant does describe these in the Specification (see below) and Applicant provides a method for determining Brittle-1 activity (see below). Further, it is not within the Examiner's authority to make determinations based on what the Examiner believes art cited in the Specification to be "not well known." (see below) A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)." MPEP 2163.04.

Applicants' claimed invention (in claim 26 and those depending therefrom) substantially conforms to Example 14 of the "Synopsis of Application of Written Description Guidelines, Revision 1", *available at* http://www.uspto.gov/web/menu/written.pdf (last visited July 1, 2009) (*hereinafter* "Written Description Guidelines"). In Example 11, the exemplary claim is directed to "A protein having SEQ ID NO:3 and variants thereof that are at least 85% identical to SEQ ID NO:2." Despite the specification's disclosure of only a single species encoding the polypeptide of SEQ ID NO: 2 (*i.e.*, SEQ ID NO: 1), and the lack of any teaching in the specification regarding which amino acid residues in SEQ ID NO: 2 are tolerable to change, the training materials indicate that the specification satisfies

the written description requirement with respect to the scope of claim 1. According to the training materials, this is so because "[w]ith the aid of a computer, one of skill in the art could have identified all of the nucleic acids that encode a polypeptide with at least 85% sequence identity with SEQ ID NO: 2."

Claim 2 in Example 11 adds "wherein the polypeptide has activity X" and this thus similar to instant claims. In the Example this claim is rejected as because the specification lacks any teaching as to which amino acid residues in SEQ ID NO: 2 can be changed while still retaining activity X, and the art lacks any recognized correlation between structure (SEQ ID NO: 2 domains) and function (activity X), the training materials indicate that the specification fails to satisfy the written description requirement with respect to the scope of claim 2.

Applicant provides significantly more guidance for one skilled in the art than is present in Example 11. The claimed nucleotide sequences encode proteins having 95% identity to SEQ ID NO:18, with the encoded proteins having brittle-1 activity. Like Example 14, there is not substantial variation in the encoded proteins, because the entire genus must have 95% sequence identity to SEQ ID NO:18 and have brittle-1 activity. Procedures for producing proteins having 95% identity to SEQ ID NO:18 are well-known in the art as described in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, 1989 (cited in Applicants' Specification at page 14, lines 9-12). Further, Applicants provided a brittle-1 assay from Shannon *et al.*, Plant Physiol. 117:1235-52 (1998), used to identify the proteins having 95% sequence identity to SEQ ID NO:18 that also have brittle-1 activity (further discussed in enablement rejection section below) that was available to one skilled in the art at the time of filing. This is sufficient to fulfill all legal requirements under 112 as It is well-established that an applicant need not disclose that which is known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Applicants' citation of this reference in the Specification is sufficient evidence of written description of the assay (see further argument on this point under enablement).

Applicants thus respectfully submit, in accordance with Example 11 of the Written Description Guidelines, that the claimed invention is supported by sufficient written description in Applicants' Specification.

Examiner further argues that "The correlation between DNA sequences and Brittle-1 activity is not well known, and not described in the specification." Advisory Action. This is objectively untrue as Applicant does teach this in the Specification, but even if not taught by Applicant, Applicant is not legally required under the standards put forward by the Office in their guidance or BPAI decisions to teach this as it was known in the art at the time of filing. Applicant does in fact teach these elements at Figure 1 of Applicants' specification which provides a sequence comparison between SEQ ID NO:18 and a known brittle-1 protein (SEQ ID NO:21) that has only 57.3% identity to the claimed sequence, which provides a clear picture of regions of brittle-1 proteins that have high homology, and are thus likely more susceptible to modification, and regions having low or no homology where more modifications can be made.

Finally, the Board's recent decision in *Ex parte Kubin*, Appeal 2007-0819 (BPAI May 31, 2007), *available at* http://www.uspto.gov/web/offices/dcom/bpai/prec/fd070819.pdf (last visited Oct. 9, 2007), when applied to the instant facts argues that Applicant does in fact fulfill the Written Description requirement. In *Kubin*, the claim at issue was directed to "An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48." *Kubin*, Appeal 2007-0819, at 3. The *Kubin* specification "does not disclose any variants in which the nucleotide sequence encoding amino acids 22-221 of SEQ ID NO:2 is varied." *Id.* at 13 (emphasis added). In the instant case Applicant DOES disclose variants and comparisons (see above and Specification, for example, at Figure 1). Further, the Board noted that there was no disclosure of "correlation between function (binding to CD48) and structure responsible for binding to CD48 (other than the entire extracellular domain) such that the skilled artisan would have known what modifications could be made . . . without losing function." *Id.* In light of these facts, the Board concluded that "[p]ossession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." *Id.* at 16 (citing *Univ. of Rochester v. GD Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004)). Of particular concern

was Appellants failure to "describe[ ] what domains of [SEQ ID NO:2] are correlated with the required binding to CD48, and thus [Appellants] have not described which . . . amino acids can be varied and still maintain binding." *Id.*

Applicants' Specification, however, provides sufficient guidance as to what amino acids could be modified without affecting brittle-1 activity. While the Examiner has focused on lack of disclosure of sequences having 95% plus identity to SEQ ID NO:18, Figure 1 of Applicants' Specification provides a sequence comparison between SEQ ID NO:18 and a known brittle-1 protein (SEQ ID NO:21) that has only 57.3% identity to the claimed sequence, which provides a clear picture of regions of brittle-1 proteins that have high homology, and are thus likely more susceptible to modification, and regions having low or no homology where more modifications can be made. For example, at the N-termini of these sequences, ten of the first 11 amino acids are identical, with the lone difference being a conservative amino acid substitution of the valine at amino acid seven of SEQ ID NO:21 to an alanine in SEQ ID NO:18. *See, e.g.*, Wu T.D. & Brutlag D.L., Proc. Int. Conf. Intell. Syst. Mol. Biol. 4:230-40 (1996). To the skilled artisan, the significant sequence identity at the N-terminus indicates that little or no sequence substitution should be made there, and if made that conservative substitutions would be preferred, in order to maintain brittle-1 activity. Another example of high homology is amino acids 137-219 of SEQ ID NO:21 and amino acids 125-207 of SEQ ID NO:18. Of these 83 amino acids, only six are different. Four of these substitutions are conservative (two glutamines to arginines, an asparagine to threonine, and a phenylalanine to tyrosine), while two are non-conservative (an isoleucine to serine and a threonine to proline). Other regions of high homology, for example amino acids 228-418 of SEQ ID NO:21 and amino acids 216-404 of SEQ ID NO:18, provide further guidance as to where and what type of substitution could be made.

By contrast, the C-termini of these proteins are significantly different. After amino acid 404 of SEQ ID NO:18 and amino acid 418 of SEQ ID NO:21, not only does SEQ ID NO:18 contain 11 additional amino acids compared to SEQ ID NO:21, but there is also very little sequence homology between the two sequences. Thus, the skilled artisan could expect that amino acid substitutions, deletions, and/or additions in this region would have little effect on brittle-1 activity as compared to, for

example, the N-terminal regional. Another region of low sequence homology can be found at amino acids 54-136 of SEQ ID NO:21 and amino acids 61-124 of SEQ ID NO:18. Similar to the C-termini of SEQ ID NOs: 18 and 21, there is a significant difference in amino acid count in this region (83 amino acids for SEQ ID NO:21 and 64 amino acids for SEQ ID NO:18). The skilled artisan could thus conclude that this region of brittle-1 proteins can have significant amino acid substitutions, deletions, and/or substitutions yet still retain brittle-1 activity. Applicants thus submit that the specification provides sufficient guidance as to what regions of SEQ ID NO:18 could be modified and in what way to produce a protein having (1) at least 90% identity to SEQ ID NO:18 and (2) have brittle-1 activity.

Consequently, *Kubin* does not compel a result of lack of written description here and, indeed, should support Applicants' assertion of adequate written description for the claimed invention because Applicants have described a correlation between structure and function for SEQ ID NO:18. *Cf. Kubin*, Appeal 2007-0819, at 17 ("Without a correlation between structure and function, [Appellants'] claim does little more than define the claimed invention by function.").

In light of the above arguments, Applicants respectfully request withdrawal of the rejections of claims 26 and 30-40 under 35 U.S.C. § 112, first paragraph, written description.

B. Claims 26-29 are Enabled Under 35 U.S.C. § 112, 1st Paragraph.

Applicant assumes that based on the argument in the Advisory Action that only independent claim 26 (and those depending threrefrom) are rejected under 112 as the Applicant has clearly provided a sequence 100% identical to itself (see claim 30) and thus provided both Written description and Enablement for that claim under even the incorrect standard currently posited by the Office.

Claims 26-29 stand rejected under 35 USC 112, first paragraph, because the Applicants' Specification while being enabling for nucleic acids encoding a SEQ ID NO: 18 and constructs and vectors comprising them, allegedly does not reasonably provide enablement for nucleic acids encoding a protein with 95% identity to SEQ ID NO: 18 and constructs and vectors comprising them. During prosecution, the Examiner asserted that "[t]he instant specification fails to provide guidance for how to

make or isolate nucleic acids encoding proteins with 90% identity to SEQ ID NO:18—specific hybridization or PCR conditions, probes or primers are not recited." Non-Final OA, at 3, essentially re-recited in the Advisory Action. Further, the Examiner asserted that "[t]he instant specification fails to teach essential regions of the encoded protein." Non-Final OA at 3-4. The office admits that the Applicant has enabled an enzyme with 100% identity to the recited sequence. Advisory Action.

Applicants agree with the Examiner that a specification must enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. Applicants respectfully submit, however, that the Examiner's conclusion of nonenablement of sequences having 95% identity to SEQ ID NO:18 is erroneous because any experimentation needed to practice the present invention would be routine. "[A] patent specification complies with the statute even if a 'reasonable' amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be 'undue.'" *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed. Cir. 1999).

Kubin also supports Applicants' enablement arguments. As noted above, the *Kubin* Appellants claimed polynucleotides encoding polypeptides having 80% identity to a defined amino acid sequence, which has a defined binding activity. *Kubin*, Appeal 2007-0819, at 3. In Appellants' specification, the Board found that Appellants' specification taught how to make variants of the defined amino acid sequence, how to calculate identity between the defined amino acid sequence and the variants, and how to test the variant for the claimed binding activity. *Id.* at 13. The specification did not disclose, however, which amino acids could be changed and still retain the claimed activity, and it did not disclose any actual variants of the defined amino acid sequence. *Id.* The examiner in *Kubin* rejected the claims as lacking enablement for sequences having identity to the defined amino acid sequence because of the absence of working examples and because changes in defined amino acid sequence might alter the function of the variant as compared to the defined amino acid sequence. *Id.* at 10. The examiner there also noted the unpredictability of the molecular biology art. *Id.* at 13. In finding enablement of the claimed invention, the Board agreed with the examiner that the molecular biology art

was unpredictable (*Wands* factor 7), but "the other *Wands* factors weigh[ed] in Appellants' favor, particularly the state of the art and the relative skill of those in the art as evidenced by the prior art teachings and Appellants' Specification." *Id.* at 14 (internal citations and markings omitted). Further, the Board noted that "[t]he amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art." *Id.* (emphasis added). Like the *Kubin* Appellants, Applicants here provided teachings on how to make variants of SEQ ID NO:18 (*see, e.g.,* Applicants' Specification at page 15, line 4 – page 16, line 22), described how to calculate the sequence identities between SEQ ID NO:18 and its variants (*see, e.g.,* Applicants' Specification at page 8, line 34 – page 9, line 17), and provided the Shannon assay to test for brittle-1 activity. Thus, *Kubin* dictates that Applicants' claims are enabled.

Applicants further note that, if Applicants' claimed invention is limited to only those nucleotide sequences encoding SEQ ID NO:18 as suggested by the Examiner, Applicants' patent rights become essentially useless because the skilled artisan could simply modify one amino acid of SEQ ID NO:18 (the sequence of which is undisputedly disclosed in Applicants' Specification), confirm brittle-1 activity by the Shannon assay (undisputedly referenced in Applicants' Specification), yet be outside the scope of the Applicants' claims even though Applicants' Specification disclosed the complete roadmap to working around the exceptionally narrow claims. In essence, the Examiner's scope of enablement rejection produces the absurd result of Applicants' Specification enabling the skilled artisan to avoid infringement of claims covering only nucleotide sequences encoding SEQ ID NO:18, but the same specification failing to enable the same skilled artisan to produce the same modified amino acid sequence if the claims cover sequences having 90% identity to SEQ ID NO:18.

Applicants also believe that any of the arguments presented in the enablement section should be applicable towards establishing that sufficient written description was present in Applicants' Specification as filed and vice versa. As noted in *LizardTech*, "a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor

possesses the full scope of the invention, and vice versa." 434 F.3d at 1345, 76 USPQ2d at 1733. That the present specification supports possession (written description) of the genus of polypeptides encompassed by the present claims (see above) further evidences enablement of the present claims. All methods for generating the described polypeptide variants were standard in the art at the time of filing. Likewise, methods for testing for the required activity were described in Applicants' Specification (see above). Thus, the possessed genus is enabled, almost by definition.

In view of the foregoing, Applicants respectfully request withdrawal of the Section 112, 1st paragraph, enablement rejections.

B. Claims 26-29 are Obvious Under 35 U.S.C. § 103.

The Federal Circuit has clearly spoken on obviousness and how it is to be applied in the recent *In re Kubin* (Fed. Cir. 2008-1184, serial number 09/667859) decision. The Office did not have the benefit of that decision and Applicant assumes the Office would not argue that, as it did in the Advisory Action, that "it would be obvious to one of skill in the art to isolate the wheat brittle-1 gene (sic) better study starch synthesis and the function of the protein; further it would be obvious to isolate it to procure another transit peptide that targets proteins to the inner amyloplast." Advisory Action.

Applicant has argued previously that Sullivan does "not teach nucleic acids that encode brittle-1 proteins with 90% or 95% identity to SEQ ID NO: 18." Response to Final Office Action. Applicant believes that the sequence of the wheat gene cannot be anticipated by a general statement that it would be obvious "to isolate homologues" based on a sequence from another plant (this conclusion is supported by *Ex Parte Kubin*, see below). The claims are specifically limited to the sequence of the wheat gene, or those sequences 95% similar, and this specific sequence (the wheat gene) cannot be anticipated by a general statement. A prima facie case of obviousness can be found where a chemical compound has close structural similarity as would have been obvious to one skilled in the art (MPEP2144.09), but since the structural similarity between DNA and protein sequences is unpredictable

in foresight, Applicant believes this art, or combination thereof, does not make this invention obvious and that the Office has used hindsight reconstruction.

Further, Sullivan provides no motivation to search for a monocot Brittle-1 different from the maize gene in Sullivan. Sullivan simply clones corn genes, and does not state or imply a need in the art to search for genes from other sources." Response to Office Action, March 3, 2009 beginning at page 4 line 29.

Applicant believes those arguments are still persuasive, and both are bolstered by the Federal Circuit in *Kubin*. The *Kubin* facts include a "isolated from a cDNA library . . . using the commercial monoclonal antibody C1.7 . . . disclosed by Valiante." *Id* at 6 citing Ex parte Kubin, No. 2007-0819 (B.P.A.I. May 31, 2007) at 5. The instant facts are completely different. In the instant facts the Office is saying that in a situation where you have a gene in one plant (isolated by Sulllivan) that the presence of that gene makes a gene, with a different and unpredictable composition, in another organism obvious. If the BPAI were to hold this, it would be a huge expansion of the obviousness doctrine in unpredictable arts and make essentially all genetic elements obvious, as a homologue for nearly every gene in existence is known. The homologues found herein have unpredictable specific sequences and are difficult to isolate. It is, in fact, very hard to determine with any specificity what is the most direct homologue to any gene in one organism in another organism.

Additionally, the *Kubin* facts show a specific motivation to isolate the gene of interest. *Id* at 17. Herein, the Office can point to no specific motivation in any reference, The Office has instead created the motivation to combine completely from the Examiner's mind.

If the Sullivan reference does not make the instant invention obvious, then the obviousness rejection falls as the Li reference does not make the sequence obvious. The Li reference also does not provide any motivation to isolate the gene of the instant invention, as the Office has not argued such.

In view of the foregoing, Applicants respectfully request withdrawal of the obviousness rejection.

VIII. CONCLUSION

For the reasons set forth above, the Board is respectfully requested to reverse the final rejection of pending Claims 26-30 and indicate allowability of all claims.

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CLAIMS APPENDIX

26. An isolated polynucleotide comprising:

(a) a nucleotide sequence encoding a polypeptide having brittle-1 activity, wherein the polypeptide has an amino acid sequence of at least 95% sequence identity when compared to SEQ ID NO:18, or

(b) a full-length complement of the nucleotide sequence of (a).

27. The isolated polynucleotide of Claim 26, wherein the polypeptide has a sequence identity of at least 95%, based on the Clustal method of alignment, when compared to SEQ ID NO:18.

28. A recombinant DNA construct comprising the polynucleotide of Claim 26 operably linked to a regulatory sequence.

29. A vector comprising the polynucleotide of Claim 26.

30. An isolated polynucleotide comprising:

(a) a nucleotide sequence encoding a polypeptide having brittle-1 activity, wherein the polypeptide has an amino acid sequence of at least 100% sequence identity when compared to SEQ ID NO:18, or

(b) a full-length complement of the nucleotide sequence of (a).

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None